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# Role of cardiac biomarkers in cognitive impairment and functional decline

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# CHAPTER 3

# HEART RATE VARIABILITY AND COGNITIVE IMPAIRMENT

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## Abstract

**Objective:** To investigate the cross-sectional and longitudinal associations of 10-second heart rate variability (HRV) with various domains of cognitive function in older participants at risk of cardiovascular disease. **Methods:** We studied 3,583 participants, mean age of 75.0 years, who were enrolled in the Prospective Study of Pravastatin in the Elderly at Risk. From baseline 10-second ECGs, standard deviation of normal-to-normal intervals was calculated as the index of HRV. Four cognitive domains were assessed at baseline and repeated during a mean follow-up period of 3.2 years. **Results:** Lower HRV at baseline was associated with worse performance in reaction time (mean difference between low third vs high third of HRV 5 1.96 seconds, 95% confidence interval [CI] 0.20 to 3.71) and processing speed (20.57 digits coded, 95% CI 21.09 to 20.05). During follow-up, participants with lower HRV had a steeper decline in processing speed (mean annual change between low third vs high third of HRV 5 20.16 digits coded, 95% CI 20.28 to 20.04). There was no difference in annual changes of reaction time or immediate and delayed memory among HRV thirds during follow-up. All these associations remained unchanged after adjustment for medications, cardiovascular risk factors, and comorbidities. **Conclusions:** Participants with lower 10-second HRV have worse performance in reaction time and processing speed and experience steeper decline in their processing speed, independent of medications, cardiovascular risk factors, and comorbidities

## Introduction

Heart rate variability (HRV), the variation in consecutive heart beat intervals, results from the constant interaction between the sympathetic and parasympathetic arms of the autonomic nervous system[1]. Reduced HRV is shown to be a strong predictor of cardiovascular morbidity and mortality[2, 3]; and has been linked to several vascular risk factors such as hypertension, diabetes mellitus and subclinical inflammation[4].

Current evidence indicates that vascular risk factors are independently associated with cognitive impairment in older participants. Cardiovascular risk factors and morbidities contribute to the development of cognitive impairment possibly by affecting the neurovascular integrity of the brain[5]. Neurovascular integrity of the brain is dependent on adequate and constant cerebral blood flow and regulation of cerebral blood flow requires intact function of autonomic nervous system[5, 6]. Hence, participants with lower HRV, as a reflection of autonomic dysfunction, might be at increased risk of cognitive decline.

HRV is typically measured using long or short-term electrocardiogram (ECG) recordings. Long-term measurements provide detailed information during physiological conditions such as activity and rest. Despite merits of long-term measurements, they are time-consuming and involve patients' discomfort which might limit their application in routine clinical practice. On the other hand, measuring HRV from a 10-second ECG recording is more practical and easier to apply in daily practice. It has been suggested that 10-second HRV may predict 5-minute cardiac vagal tones accurately[7]; and has a comparable predictive value for cardiac mortality in older participants[8]. However, to date there is no study evaluating the association of HRV with cognitive function using 10-second HRV measurements. In this study, we assessed the cross-sectional and longitudinal association of HRV, using 10-second ECG recordings, with various domains of cognitive function in older participants at high risk of cardiovascular disease.

## Methods

### *Study Design and participants*

The data for this study were drawn from PROSPER (PROspective Study of Pravastatin in the Elderly at Risk), a large prospective study of 5804 men and women aged 70 to 82 years. PROSPER was a randomized controlled trial designed to examine the effect of pravastatin in older participants with pre-existing or at high risk of cardiovascular diseases. The mean follow-up time was 3.2 years. The PROSPER study design, inclusion and exclusion criteria have been described elsewhere[9, 10]. We received approval from the institutional ethics review boards of the three centers on human experimentation and the PROSPER study complied with the Declaration of Helsinki. All participants in the study provided written informed consent[10].

In this study, we excluded all participants with cardiac arrhythmias and/or cardiac rhythms not generated by the sino-atrial node including premature ventricular and/or atrial contractions (n=414), ectopic atrial rhythm (n=161), supraventricular arrhythmia (n=139), atrial fibrillation (n=89), atrial flutter (n=13) and other arrhythmias (n=85) from the original PROSPER cohort. Individuals with sinus arrhythmia were also excluded (n=314). Furthermore, participants with missing HRV measurements at baseline (n=148) and with missing cognitive measurements at baseline or during follow-up (n=858) were excluded. Accordingly, 3583 participants were included in this study. Included participants were slightly younger and had lower degrees of cardiovascular co-morbidities (table e-1). We included participants from both pravastatin and placebo groups as it has been shown that treatment with pravastatin does not affect cognitive function[11]. Moreover, we adjusted our analyses for pravastatin treatment groups.

### *HRV measurements*

Standard 10-second ECG recordings were obtained in resting, supine position using a Burdick Eclipse 850i electrocardiograph in the morning of the first enrolment visit before initiation of

statin treatment. These digital data were subsequently transferred to the University of Glasgow ECG Core Lab based at Glasgow Royal Infirmary, Scotland, for storage[12]. HRV was measured using the University of Glasgow resting ECG program – a fully automated method – to ensure the reproducibility of the measurements and interpreted using the same software[13]. We used one of the most frequently used and easily calculated time domain measurements of HRV defined as the standard deviation of normal-to-normal R-R intervals (SDNN) in the 10-second ECG recording period. For each ECG, the onset of every QRS complex was recorded and then the dominant or normal-to-normal R-R intervals were calculated. Dominant R-R intervals are defined as the time between two normally conducted QRS complexes. The standard deviation of dominant R-R intervals was calculated thereafter.

*Cognitive function measurements*

The mini-mental state examination (MMSE) was used to measure global cognitive function at baseline. The cutoff point of 24 or more was applied as the inclusion criterion and participants with poor cognitive function (MMSE < 24) were excluded from enrolment in PROSPER. In this study, we used four neuropsychological performance tests to assess different domains of cognitive function. The Stroop test was used to assess selective attention and reaction time. The outcome variable was the time (number of seconds) taken to complete the test, with higher scores indicating worse performance. The Letter-Digit Coding test was used to measure the general cognitive processing speed. The outcome variable was the total number of correct digits entered in 60 seconds; a higher score indicates better performance. Memory was assessed using the Picture-Word Learning Test, which tests the immediate and delayed memory. The outcome variable was the accumulated number of correctly recalled pictures over 3 trials and the number of pictures recalled during delayed recall; a higher score indicates better performance. The test/re-test correlation of Stroop and Letter-Digit Coding tests were shown to be high (r = 0.80 and 0.88, respectively). The reliability of immediate and delayed Picture-Word Learning tests were shown to be acceptable (r = 0.66 and 0.63, respectively). In addition, the test/re-test correlations were independent of age and education[14]. Cognitive function was measured at baseline, after 9,

18 and 30 months, and at the end of the study. The time point at the end of the study varied among participants and ranged from 36 to 48 months.

*Statistical analyses*

Baseline characteristics of participants are reported as mean (SD) for continuous variables and as number of participants (%) for categorical variables across thirds of HRV. To test the cross-sectional and longitudinal association of HRV and cognitive domains, we used linear regression models. In longitudinal analyses, regression coefficient of the change in each cognitive test score per year was calculated for each participant, which indicates the annual changes in cognitive domains during follow-up time. This allowed us to test the longitudinal associations more accurately by using repeated measurements of cognitive tests. In both cross-sectional and longitudinal analyses, probability values were calculated using continuous log-transformed values of baseline SDNN as the determinant, since it was not normally distributed. Using analysis of covariance, we calculated the adjusted mean values of baseline and annual changes of cognitive scores in thirds of HRV.

All cross-sectional and longitudinal analyses were performed in 2 steps. In the first step (minimally adjusted model), the analyses were adjusted for age, sex, education (age at which the participants left school), country of enrolment and version of cognitive tests where appropriate. In the second step (fully adjusted model), the analyses were further adjusted for cardiovascular risk factors and morbidities and use of antihypertensive medications. In the longitudinal analyses, both models were additionally adjusted for baseline cognitive domain scores, and the fully adjusted model was additionally adjusted for statin treatment.

To explore the effect of cardiovascular events on the longitudinal associations, we performed a series of additional analyses in which we stratified for participants who did and did not develop incident stroke, incident heart failure hospitalization and incident coronary events. To test whether the difference between participants who did and did not develop cardiovascular events is significant, *p* value for interaction was calculated using linear regression models. To test whether the association of HRV with cognitive domains is

independent of ß-blockers and medications with antiarrhythmic or anticholinergic properties, the longitudinal analyses were repeated after exclusion of participants who used those medications. Finally, to check whether the relation between HRV and cognitive domains is independent of heart rate, the cross-sectional and longitudinal analyses were repeated after standardizing HRV for heart rate (SDNN was divided by heart rate)[15]. A *p* value of < 0.05 was considered as statistically significant.

## Results

The mean age of the study population was 75.0 years and 1675 (46.7%) participants were male. Median HRV as measured by SDNN was 17.00 milliseconds. Table 1 shows the baseline characteristics of participants in thirds of HRV. Participants in the lowest third of HRV were older, had higher resting heart rate, higher body mass index and used beta-blockers less frequently (all *p* values < 0.05).

Table 2 shows the cross-sectional association of HRV with cognitive domains in the minimally adjusted model. At baseline, participants with lower HRV had worse performance on the Stroop test (mean score of 64.71 seconds in the lowest third, 64.46 seconds in the middle third, and 62.75 seconds in the highest third, $p = 0.008$) and the Letter-Digit Coding test (mean score of 23.62 digits coded in the lowest third, 23.67 digits coded in the middle third, and 24.18 digits coded in the highest third, $p = 0.008$). Lower HRV was not associated with worse performance in the immediate and delayed Picture-Word Learning tests. Figure 1 shows the cross-sectional association of HRV with cognitive domains after full adjustment for medications, cardiovascular risk factors, and comorbidities. Full adjustments did not change the cross-sectional results, meaning that lower HRV remained associated with worse performance in the Stroop and Letter-Digit Coding tests.

**Table 1.** Baseline characteristics of participants in thirds of heart rate variability

| | Thirds of SDNN, ms | | | |
|---|---|---|---|---|
| | Low n = 1197 | Middle n = 1193 | High n = 1193 | *p* Value |
| *Socio-demographics* | | | | |
| Age, y , mean (SD) | 75.24 (3.38) | 74.98 (3.25) | 74.92 (3.28) | 0.047 |
| Male, n (%) | 553 (46.2) | 563 (47.2) | 559 (46.9) | 0.885 |
| Age left school, y, mean (SD) | 15.23 (2.09) | 15.24 (2.14) | 15.15 (2.11) | 0.507 |
| *Cardiovascular risk factors* | | | | |
| HR, beats/min, mean (SD) | 70.01 (11.71) | 64.80 (10.40) | 61.71 (9.80) | <0.001 |
| History of stroke or TIA, n (%) | 136 (11.4) | 131 (11.0) | 106 (8.9) | 0.103 |
| History of MI, n (%) | 146 (12.2) | 140 (11.7) | 153 (12.8) | 0.718 |
| History of DM, n (%) | 143 (11.9) | 127 (10.6) | 108 (9.1) | 0.070 |
| SBP, mm Hg, mean (SD) | 155.87 (21.4) | 154.52 (22.8) | 153.17 (21.3) | 0.010 |
| DBP, mm Hg, mean (SD) | 84.6 (11.0) | 84.0 (11.6) | 82.6 (10.8) | <0.001 |
| BMI, kg/m $^2$ ,mean (SD) | 27.21 (4.2) | 26.83 (4.1) | 26.74 (4.0) | 0.015 |
| Current smoking, n (%) | 286 (23.9) | 325 (27.2) | 323 (27.1) | 0.110 |
| *Antihypertensive medications* | | | | |
| ß-blockers, n (%) | 283 (23.6) | 337 (28.2) | 366 (30.7) | <0.001 |
| Calcium channel blocker, n (%) | 303 (25.3) | 303 (25.4) | 301 (25.2) | 0.996 |

Abbreviations: BMI: body mass index; DBP: diastolic blood pressure; DM: diabetes mellitus; HR: heart rate; MI: myocardial infarction; SBP: systolic blood pressure; SDNN: standard deviation of normal-to-normal R-R intervals. The differences in characteristics across thirds of SDNN were examined using analysis of variance test for continuous variables and $x^2$ test for categorical variables.

Table 3 shows the association of baseline HRV and changes in cognitive domains during a mean follow-up of 3.2 years. In the minimally adjusted model, participants with lower HRV had a steeper decline in the Stroop test performance (mean annual change of 1.63 seconds in the lowest third, 0.96 seconds in the middle third and 1.11 seconds in the highest third), although this association was marginal ($p$ = 0.073). Similarly, participants with lower HRV had a steeper decline in the Letter-Digit Coding test score (mean annual change of −0.50 digits coded in the lowest third, −0.49 digits coded in the middle third and −0.35 digits coded in the highest third, $p$ = 0.016). In contrast, low HRV was not associated with accelerated decline in the immediate and delayed Picture-Word learning test scores during follow-up. After full adjustment for cardiovascular risk factors, co-morbidities and use of medications, the

estimates of the difference in cognitive domains between the HRV groups did not change essentially. Lower HRV remained associated with a steeper decline in the Letter-Digit coding test score ($p$ = 0.038), whereas for the Stroop test and the immediate and delayed Picture-Word learning tests, the associations did not reach statistical significance ($p$ value = 0.084, 0.337 and 0.738, respectively).

**Table 2.** Baseline cognitive domains in relation to heart rate variability

| | Thirds of SDNN, ms | | | |
|---|---|---|---|---|
| | Low (1.70-12.60) n = 1197 | Middle (12.70-22.90) n = 1193 | High (23.00- 128.40) n = 1193 | *p V*alue[a] |
| Stroop, s | 64.71 (0.63) | 64.46 (0.63) | 62.75 (0.63) | 0.008 |
| LDCT, digits coded | 23.62 (0.19) | 23.67 (0.19) | 24.18 (0.19) | 0.008 |
| PLTi, pictures remembered | 9.44 (0.05) | 9.38 (0.05) | 9.47 (0.05) | 0.353 |
| PLTd, pictures remembered | 10.28 (0.07) | 10.26 (0.07) | 10.41 (0.07) | 0.130 |

Abbreviations: LDCT: Letter-Digit Coding Test; PLTd: Picture-Word Learning Test delayed; PLTi: Picture-Word Learning Test immediate; SDNN: standard deviation of normal-to-normal R-R intervals. Data represent mean score (standard error) of each cognitive test. Adjusted for country, age, sex, education, and version of LDCT and PLT tests. [a] The $p$ values were calculated using the continuous values of log-transformed SDNN.

In additional analyses, we combined the lowest and the middle thirds of HRV and repeated the cross-sectional and longitudinal analyses. Results show that compared to the high HRV group, the combined middle and low HRV group was associated with worse performance in the Stroop and the Letter-Digit Coding test (table e-2). The longitudinal results indicate that the combined middle and low HRV thirds is associated with a steeper decline on the Letter-Digit Coding test and the immediate Picture-Word Learning test (table e-3).

**Table 3.** Annual changes of cognitive domains in relation to heart rate variability

| | Thirds of SDNN, ms | | | |
|---|---|---|---|---|
| | Low n = 1197 | Middle n = 1193 | High n = 1193 | *p* Value[a] |
| *Stroop, s* | | | | |
| Minimally adjusted model | 1.63 (0.30) | 0.96 (0.30) | 1.11 (0.30) | 0.073 |
| Fully adjusted model | 1.62 (0.30) | 0.94 (0.30) | 1.13 (0.30) | 0.084 |
| *LDCT, digits coded* | | | | |
| Minimally adjusted model | −0.50 (0.04) | −0.49 (0.04) | −0.35 (0.04) | 0.016 |
| Fully adjusted model | −0.50 (0.04) | −0.49 (0.04) | −0.35 (0.04) | 0.038 |
| *PLTi, pictures remembered* | | | | |
| Minimally adjusted model | −0.06 (0.02) | −0.05 (0.02) | −0.01 (0.02) | 0.257 |
| Fully adjusted model | −0.06 (0.02) | −0.05 (0.02) | −0.01 (0.02) | 0.337 |
| *PLTd, pictures remembered* | | | | |
| Minimally adjusted model | −0.11 (0.03) | −0.10 (0.03) | −0.09 (0.03) | 0.698 |
| Fully adjusted model | −0.11 (0.03) | −0.10 (0.03) | −0.10 (0.03) | 0.738 |

Abbreviations: LDCT: Letter-Digit Coding Test; PLTd: Picture-Word Learning Test delayed; PLTi: Picture-Word Learning Test immediate; SDNN: standard deviation of normal-to-normal R-R intervals. Data represent mean annual change (standard error) in each cognitive test. Minimally adjusted model: adjusted for country, age, sex, education, cognitive scores at baseline, and version of LDCT and PLT tests. Fully adjusted model: adjusted for country, age, sex, education, baseline cognitive scores, version of LDCT and PLT tests, body mass index, smoking, systolic blood pressure, diastolic blood pressure, history of stroke/TIA, history of myocardial infarction, history of diabetes mellitus, statin treatment, and antihypertensive medications (diuretics, ß-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers).[a]The p values were calculated using the continuous values of log-transformed SDNN.

Figure 2 shows the association of HRV with cognitive decline, stratified by cardiovascular events during follow-up including stroke or TIA (n=199), heart failure hospitalization (n=78) and coronary events (n=269). There was no difference in change of cognitive domains during follow-up between participants who did and did not develop cardiovascular events (all *p* for interaction >0.05). Likewise, stratification of participants based on the presence of history of stroke or TIA at baseline did not change the longitudinal results (data not shown).

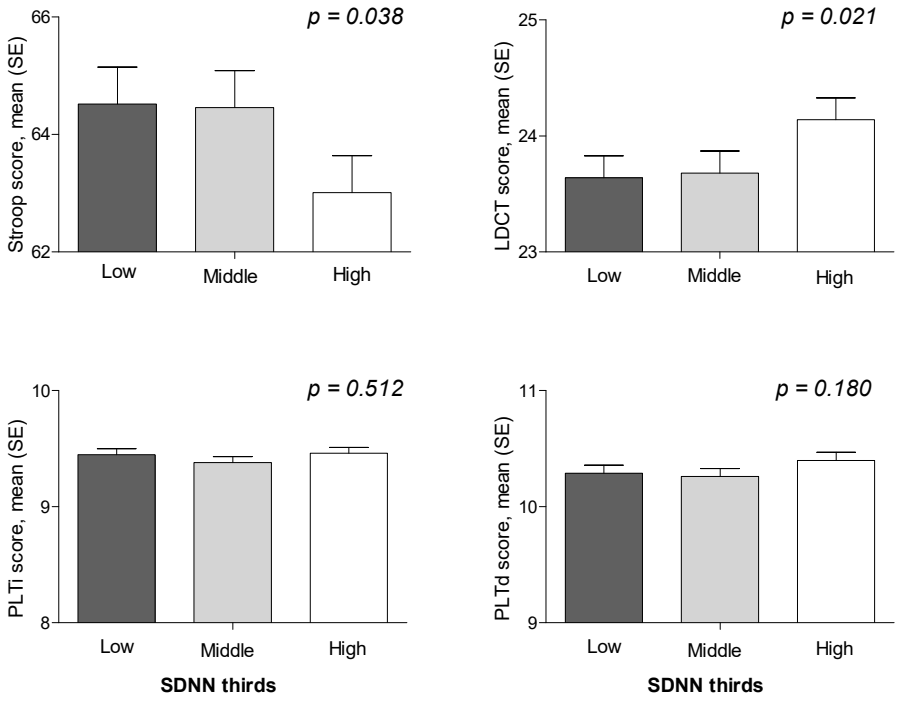


**Figure 1. Baseline cognitive domains in relation to heart rate variability in the fully adjusted model.** All analyses were performed in the fully adjusted model. PLTd: Picture-Word Learning Test delayed; PLTi: Picture-Word Learning Test immediate; SDNN: standard deviation of normal-to-normal R-R intervals.

Furthermore, the sensitivity analyses after exclusion of participants who used β-blockers (n = 986) and medications with antiarrhythmic (n = 75) or anticholinergic (n = 98) properties did not change the associations between HRV and cognitive decline (table e-4). After exclusion of participants who used β-blockers (n = 986, 27.5% of the population), the association between HRV and Letter-Digit Coding test scores remained essentially the same, with marginal *p* values (table e-4). Finally, standardization of SDNN for heart rate did not change the cross-sectional and longitudinal results (table e-5 and 6).

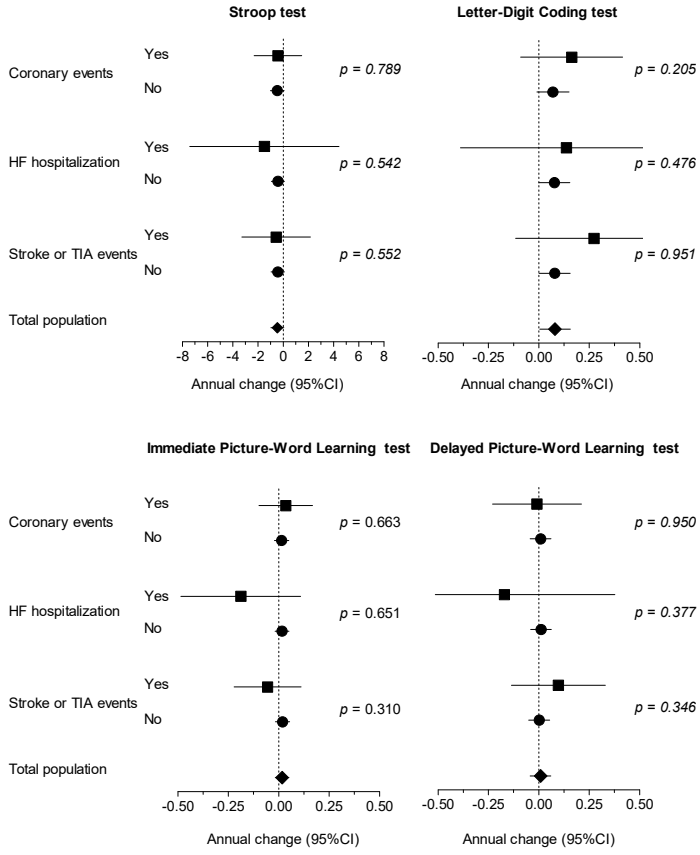


**Figure 2. Annual changes of cognitive domains in relation to heart rate variability, stratified for cardiovascular events during follow-up.** Data represent annual change (95% CI) per 1 millisecond increase in log-transformed SDNN for each cognitive test, stratified by cardiovascular events during follow-up. Adjusted for country, age, sex, education, version of cognitive tests, BMI, smoking, systolic blood pressure, diastolic blood pressure, history of stroke/TIA, history of myocardial infarction, history of diabetes mellitus, statin treatment, and antihypertensive medications. The p values show p for interaction. HF: heart failure.

## Discussion

In this study, we show that older participants at risk of cardiovascular disease with lower 10-second HRV have worse performance in reaction time and processing speed and experience

steeper decline in their processing speed during a mean period of 3.2 years. These associations were independent of cardiovascular risk factors and morbidities.

Our findings are in line with some studies on the association between HRV and cognitive function. For example, cross-sectional results from 869 Mexican Americans with a mean age of 75 years have shown that reduced 5-minute HRV was associated with worse performance on the MMSE test, but not with verbal memory[16]. Results from the Vietnam Era Twin Registry on healthy middle aged men showed that reduced 24-hour HRV was associated with poor verbal, but not visual and memory performance[17]. The cross-sectional results from the Irish longitudinal study on ageing (TILDA) showed that reduced 5-minure HRV was most strongly associated with worse performance in memory recall and language[18]. To date, the only prospective study on the longitudinal association between HRV and cognitive function is the UK Whitehall II study, which showed no cross-sectional and longitudinal associations[19]. However, in that study the cognitive battery used was not able to assess the executive function in details. Furthermore, their population consisted of middle-aged adults who were much younger than the PROSPER participants.

There are several explanations that might describe the observed associations between HRV and cognitive function. First, cardiovascular risk factors such as hypertension, subclinical inflammation and diabetes mellitus have been linked to both reduced HRV and cognitive impairment[4, 20, 21]. This might suggest that cardiovascular risk factors play role as extraneous factors on the association between HRV and cognitive function. Nevertheless, we observed that adjustment of our analyses for several well-established cardiovascular risk factors did not change the associations. Second, reduced HRV is associated with future cardiovascular events[3, 22], which in turn might result in neurocognitive deficits and cognitive decline. We observed that the association between HRV and cognitive function was not different in participants without cardiovascular events during follow-up time. In this setting, reduced HRV might serve as an early manifestation of brain damage mirrored in disturbed autonomic nervous system. Third, low HRV as a reflection of autonomic dysfunction might directly link to cognitive impairment by causing dysregulations in cerebral perfusion[23].

Furthermore, it is possible that lower HRV might reflect established cerebral lesions and neurodegenerative processes in the brain[18]. Finally, given that low HRV have been associated with higher blood pressure variability[24] and that higher blood pressure variability has been shown to be associated with cognitive decline and structural brain changes[25, 26], it is likely that altered HRV is associated with cognitive decline by increasing blood pressure variability.

In this study, we show that reduced HRV is related to worse performance and future decline of executive function. Executive function is mainly controlled by the prefrontal cortex of the brain. It has been shown that reduced HRV is associated with hypo-activity of the prefrontal cortex, which might in turn disturb executive function[27, 28]. In a meta-analyses, Thayer and colleagues have shown that HRV is closely related to neuronal activities in the ventromedial prefrontal cortex[29]. Furthermore, it has been shown that the frontal cortex is able to adjust HRV via subcortical structures such as the amygdala. This cortico-subcortical inhibitory circuit is the structural connection between neuropsychological processes such as cognitive function and physiological processes such as HRV. Abnormalities in the cortico-subcortical circuit can be reflected in HRV[28]. In this setting, future brain imaging studies might bring new insights in the biology of observed associations.

The selective association of lower HRV with cognitive domains involving speed needs further exploration. Previously, it has been shown that the detrimental effects of cardiovascular risk factors are more evident in such cognitive domains [30], however it is also possible that HRV is basically related to the pace of performing a certain task and not necessarily to the cognitive ability of the participants. In addition, we observed that the largest changes in cognitive scores were between the “high” HRV group and the remaining two-third of the population. It is important to mention that there is no well-established clinical cut-off value for categorization of HRV indices which might hamper grouping of participants and therefore the comparisons should be performed cautiously.

This study has certain strength and limitations. The major strengths are the large sample size and the prospective design which allowed us to examine the temporality of associations. Furthermore, we used an extensive set of neuropsychological tests consisting

of four cognitive tests to assess different domains of cognitive function. We could also show that the results are independent of cardiovascular risk factors and co-morbidities. As limitations, the participants in this study were at high risk of cardiovascular disease which makes it difficult to generalize our findings to a healthy elderly population. Nevertheless, a considerable proportion of older adults have a number of cardiovascular pathologies and our results were independent of cardiovascular risk factors, co-morbidities and use of medications. Using a 10-second HRV might serve as a possible limitation as it does not allow capturing the circadian changes. However, we were able to show that reduced HRV associates with cognitive impairment even by using 10-second HRV which is widely used in clinical practice and is more feasible for assessment. Another limitation could be the relatively small changes in the absolute scores of cognitive domains. This might be due to the PROSPER inclusion criteria (MMSE ≥ 24 points) resulting in participants with a relatively preserved cognitive function at baseline. Of note, although the magnitude of associations were modest, the effect estimates were comparable with the effect estimates of apolipoprotein E4 in the same population[31].

In our cohort of older participants at high risk of cardiovascular disease, participants with lower 10-second HRV have worse performance in reaction time and processing speed and experience steeper decline in their processing speed, independent of cardiovascular risk factors and co-morbidities.

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*Appendices (e-tables) are available online*:

*http://n.neurology.org/content/suppl/2016/02/18/WNL.0000000000002499.DC1*